# PATENT COOPERATION TREATY

# PCT



# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference<br>PCT 84272 | **FOR FURTHER ACTION** | See Form PCT/IPEA/416 |
|---|---|---|
| International application No.<br>PCT/IT2004/000713 | International filing date *(day/month/year)*<br>21.12.2004 | Priority date *(day/month/year)*<br>22.12.2003 |
| International Patent Classification (IPC) or national classification and IPC<br>A61K33/42, A61P19/02, A61P19/06 | | |
| Applicant<br>UNIVERSITA DEGLI STUDI DI SIENA et al. | | |

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☒ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the opinion |
| ☐ | Box No. II | Priority |
| ☐ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☐ | Box No. VIII | Certain observations on the international application |

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 21.10.2005 | 06.02.2006 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized Officer<br>Hornich, E<br>Telephone No. +49 89 2399-8721 |

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IT2004/000713

## Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   **Description, Pages**

   1-33 as originally filed

   **Claims, Numbers**

   1-23 received on 24.10.2005 with letter of 21.10.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☒ the claims, Nos. 1-23
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 7,8 |
| | No: | Claims | 1-6,9,10 |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-10 |
| Industrial applicability (IA) | Yes: | Claims | 1-10 |
| | No: | Claims | |

2. Citations and explanations (Rule 70.7):

**see separate sheet**

## SECTION I

1. **This report has been established as if the amendments had not been made**, since they have been considered to go beyond the disclosure as filed (R. 70.2(c) PCT). The reasons are as follows:

1.1 Claim 1:

Claim 1 as originally filed related to a 'soluble pharmaceutical composition for the treatment of articular pathologies comprising an effective amount of at least one linear or cyclic polymetaphosphate or a soluble and pharmaceutically acceptable salt thereof, and appropriate diluents.'

The present claim 1 relates to the 'use of a linear or cyclic polymetaphosphate or a soluble salt thereof for the preparation of an intra-articular injectable medicament for the treatment of articular pathologies.'

The reformulation of a *product-claim* as claim directed to the second medical use of the *same* product is in general acceptable. However, in this case, the features of the product have been changed:

Claim 1 as originally filed involved a 'soluble pharmaceutical composition .... comprising ... linear or cyclic polymetaphosphate or a soluble and pharmaceutically acceptable salt thereof, and appropriate diluents.'
The features '*soluble pharmaceutical composition*' and also '*and appropriate diluents*' are not any more comprised in the subject-matter of the present claim 1.
The scope of the present claim 1 relates to the 'use of a linear or cyclic polymetaphosphate or a soluble salt thereof for the preparation of an intra-articular injectable medicament', is not limited to the '*soluble pharmaceutical composition*' which also comprises '*appropriate diluents*', and is therefore broader than the scope of claim 1 as originally filed.

The same applies also to claims 20, 21 and 23 which refer to the 'substance according to claims 1-3(6)'.

1.2 Claim 8:

There is no sufficient basis for the introduction of '*antioxydant activity*' in the claim.

1.3 Claims 9-19:

The subject-matter introduced into the claims represents a generalisation of particular examples where the compounds are used in particular amounts.
The general description does not disclose these particular combinations of compounds introduced into the claims.

1.4 The scope of the claims has therefore been extended. No basis for such an extension can be found in the application as filed and hence the claims as amended result in the application being amended in such way that it contains subject-matter which extends beyond the content of the application as filed.

**SECTION V**

2. *References*:

**D1**: CINI R ET AL: "Dissolution of calcium pyrophosphate crystals by polyphosphates: An in vitro and ex vivo study" ANNALS OF THE RHEUMATIC DISEASES, vol. 60, no. 10, October 2001 (2001-10), pages 962-967, ISSN: 0003-4967
**D2**: US-A-3 541 208
**D3**: GB-A-1 132 233
**D4**: US 2002/022052 A1
**D5**: FR-A-1 077 682
**D6**: GB 817 181 A
**D7**: RYAN L M ET AL: "Stimulation of cartilage inorganic pyrophosphate elaboration by ascorbate" MATRIX 1991 GERMANY, vol. 11, no. 4, 1991, pages 276-281, ISSN: 0934-8832
**D8**: WO 00/66599 A
**D9**: US-B1-6 399 093

3. *Novelty* **(Art. 33(2) PCT)**

N.B.: The present claims 1-10 define pharmaceutical compositions / formulations. For the assessment of novelty of pharmaceutical compositions, the intended use, i.e. the particular indication for which the compositions are to be used, are *not* taken into consideration.
That is, the subject-matter of claims 1-10 discloses nothing more than the compositions / formulations per se.

3.1 **D1** discloses studies in order to determine the dissolving ability of linear pentasodium tripolyphosphate (PSTP), cyclic trisodium metaphosphate (TSMP), polymeric sodium metaphosphate (SMP) on synthetic crystals of calcium pyrophosphate dihydrate (CPPD) and on crystalline aggregates of menisci from patients with chondrocalcinosis.

The outcome of the studies suggest a potential therapeutic use of the compounds in the treatment of symptomatic chondrocalcinosis.

**D1** ***anticipates*** the subject-matter of claims 1-3 and 10.

N.B.: The tests described in **D1** were carried out *in vitro* and *ex vivo*; in the present application, the formulations were tested *in vitro* and *ex vivo*, too.

3.2 **D2** discloses that a combination of polyphosphates and silicates is useful for the treatment of *(osteo)arthritis* ('articular pathology').
'*It also prevents calcium from depositing at the joint*' (col. 1, l. 61-63).

**D2** ***anticipates*** the subject-matter of claims 1-3.

3.3 **D3** as well discloses the usefulness of e.g. *tripolyphosphate* and *hexameta-phosphate* in combination with another complexing agent for the treatment of calcific deposits in bodies by e.g. parenteral administration. Examples demonstrate the effectiveness in *polyarthritis* and *rheumatoid arthritis* ('articular pathologies').

**D3** ***anticipates*** the subject-matter of claims 1-3.

3.4 **D4** discloses transdermal or transepithelial compositions.

Furthermore, **D4** discloses compounds which are useful for the treatment of *osteoarthritis* and *joint injury* which are articular pathologies ([126-140]), among which *glucosamine sulfate, ascorbic acid, vitamins E, A, sodium pentasan polyphosphate* and *tocopherol.*
'The preferred formulation would include: ..... glucosamine sulphate, .... ascorbic acid, .... vitamins E, A and D, ....., to be incorporated into a carrier consisting of omega 3 fatty acid, almond oil, carrot oil and cosmetic oils, waxes, anti oxidants and anti microbials as used regularly in the cosmetic industry. *Sodium pentosan polyphosphate* may be included in the formulation when its use is approved by the FDA' ([137] and [140]).
It is supposed that the compositions are 'soluble'.

**D4** ***anticipates*** the subject-matter of claims 1-6, 9 and 10.

3.5 **D5** and **D6** disclose compositions comprising phosphates and antioxidants:
**D5** describes compositions comprising *trimetaphosphate* or *hexametaphosphate* and a phenolic antioxidant, e.g. *tocopherol,* and *ascorbic acid.* The compositions can be used to stabilize pharmaceutical products.

**D6** describes compositions comprising tetracycline, *trimetaphosphate, tripoly-phosphate* or *hexametaphosphate* and *ascorbic acid* for parenteral administration.

As the intended use is disregarded (see *item 2.*, 'N.B.'), the novelty of claims 1-6, 9 and 10 is ***destroyed*** by **D5** and **D6.**

4. *Inventive Step* **(Art. 33(3) PCT)**

4.1 The subject-matter of claims 7 and 8 relates to injectable formulations where the composition according to claims 1-3 and the antioxidant are housed in separate containers.

In view of what is already known in the art, as disclosed in the documents cited under *novelty*, an inventive step can***not*** be seen in the subject-matter of claims 7 and 8. The housing of two components, which are already known in combination, in different containers is a matter of routine.

4.2 The mere *combination* of a polymetaphosphate and an anti-oxidant / anti-radical of oxygen or hypochlorite anion for the manufacture of a medicament for the treatment of articular pathologies would ***not*** be considered ***inventive*** as both components are separately known for the treatment of articular pathologies (see **D1** to **D4** and **D7** to **D9**, the latter again disclosing the usefulness of ascorbic acid resp. glucosamine for the treatment of *gout*).

5. *Industrial Applicability* (**Art. 33(4) PCT**)

The requirements of industrial applicability are fulfilled for the subject-matter of claims 1-10.